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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,610	07/23/2001	Hagit Amitai	AMITAI 1	2065

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EXAMINER	
LI, RUIXIANG	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 09/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,610	AMITAI ET AL.	
	Examiner	Art Unit	
	Ruixiang Li	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,7,9-14,17 and 18* is/are pending in the application.

4a) Of the above claim(s) *13, 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,7,9-12,17 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The amendment filed on 06/04/2004 has been entered in full. Claims 1 and 9-12 have been amended. Claim 16 has been canceled. Claims 17 and 18 have been added. Claims 1, 3, 5, 7, 9-14, 17, and 18 are pending. Claims 1, 3, 5, 7, 9-12, 17, and 18 are under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Withdrawn Objections and/or Rejections

The rejection of claims 1, 3, 5, 7, 9-12, and 16 under 35 U.S.C. 112, second paragraph, as set forth in the previous Office Action (01/05/2004), has been withdrawn in view of Applicants' amendment to the claims.

The rejection of claims 9-12 and 16 under 35 U.S.C. § 103(a) as being unpatentable over Pecceu et al. (Gene, 97:253-258, 1991) and Bjorkdahl et al. (Cancer Immunol. Immunother. 44:273-281, 1997) in view of Muzio et al. (WO 9612022, April 25, 1996), as set forth in the record has been with drawn in view of Applicants' cancellation of claim 16 and amendment to claim 9.

Applicants' cancellation of claim 16 has made the rejection of the claim under 35 U.S.C. 103(a) as being unpatentable over Pecceu et al. (Gene, 97:253-258, 1991) and Selden et al. (U.S. Patent NO. 6,083,725) in view of Colotta et al. (WO 9612022, April 25, 1996) moot.

Claim Rejections Under 35 U. S. C. § 112, 1st Paragraph

(i) The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

(ii) Claims 1, 3, 5, and 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an expression vector comprising the cDNA encoding icIL-1ra-II protein and the genomic DNA sequence (SEQ ID NO: 1) that encodes a human growth hormone signal peptide, does not reasonably provide enablement for an expression vector comprising the cDNA encoding icIL-1ra-II protein and *a growth hormone signal peptide genomic DNA sequence*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims.

The factors that are considered when determining whether a disclosure satisfies enablement requirement include: (i) the quantity of experimentation necessary; (ii) the amount of direction or guidance presented; (iii) the existence of working examples; (iv) the nature of the invention; (v) the state of the prior art; (vi) the relative skill of those in

the art; (vii) the predictability or unpredictability of the art; and (viii) the breadth of the claims. *Ex Parte Forman*, 230 USPQ 546 (Bd Pat. App. & Int. 1986); *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Claim 1 recites an expression vector for the production of an icIL-1ra-II protien beginning at amino acid residue position+2 from the deduced start of translation on the icIL-1ra-II coding sequence, comprising a growth hormone signal peptide genomic DNA sequence, joined to a DNA segment encoding intracellular IL-1 receptor antagonist type II (icIL-1ra-II) and operably linked to a promoter sequence; whereas claims 3, 5, and 7 depend from claim 1 and are drawn to an isolated cell line transformed with the expression vector and a method for producing a recimbinant icIL-1ra-II comprising culturing the host cells.

The claims are broad and encompass an expression vector comprising any growth hormone signal peptide genomic DNA sequence. However, while providing sufficient guidance and/or working examples on the production of the secretory icIL-1ra-II protien with the N-terminal methionine being remomed by culturing host cells transfected with an expression vector comprising the cDNA encoding icIL-1ra-II protein and the genomic DNA sequence (SEQ ID NO: 1) that encodes a human growth hormone signal peptide (see, e.g., Examples 4-6 and 10), the specification fails to provide the sufficient guidance and/or working examples on how to make and use an expression vector comprising a growth hormone signal peptide genomic DNA sequence other than the human growth hormone signal peptide genomic DNA sequence to produce the

secretory icIL-1ra-II protien with the N-terminal methionine being remomed.

The prior art teaches the cleavage of the signal peptide and protein secretion depends upon both the sequence of the signal peptide and the amino acid residues at positions +1 and +2 of the protein being secreted (Heijne Nucleic Acid Research, 14(11): 4683-4690, 1986). However, there is no sufficent teaching in the prior art on how and what difference a genomic DNA sequence encoding a signal peptide sequence will make in expressing a secetory protein versus a cDNA sequence encoding a signal peptide sequence. Thus, the art is highly unpredictable regarding the cleavage of the signal peptide and protein secretion when an expression vector comprising a genomic DNA sequence comprising a growth hormone signal peptide. Without sufficient guidance and/or working examples, it would require undue experimentation for one skilled in the art to make and use the claimed invention commensurate in scope with the claims.

(iii) Claims 1, 3, 5, 7, and 9-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 recites an expression vector for the production of an icIL-1ra-II protein beginning at amino acid residue position +2 from the deduced start of translation on the icIL-1ra-II coding sequence, which introduces new matter because the specification

discloses two forms of icIL-1ra-II proteins—not just one form—were produced in the host cells transfected with the vector of the present invention: a mixture of icIL-1ra-II proteins beginning at amino acid residue position +2 and +1 from the deduced start of translation on the icIL-1ra-II coding sequence. Limiting the scope of the invention in this case necessarily introduces new matter. Claims 3, 5, and 7 depend upon claim 1.

Claim 9 recites an isolated icIL-1ra-II beginning at amino acid residue position +2 from the deduced start of translation on the icIL-1ra-II coding sequence and having the amino acid sequence of SEQ ID NO: 11 at the N-terminus, which introduces new matter because the specification discloses production of secretory icIL-1ra-II proteins, which are glycosylated (see, e.g., Examples 5 and 6) and there is no support for the unglycosylated portein. Moreover, the apparent molecular weight of about 27 kDa and 30 kDa on SDS-PAGE under reducing conditions with 15% acrylamide, as recited in claims 10 and 11, is described for the glycosylated icIL-1ra-II proteins (see Example 8, page 16 of the specification). The unglycosylatred icIL-1ra-II proteins have a lower molecular weight. In fact, Colotta et al. (WO 96/12022, April 25, 1996) teach the icIL-1ra-II protein that was intracellularly expressed had an apparent molecular weight of approximately 25 kDa (line 11 of page 11). Claim 12 depends on claim 9.

Claim Rejections Under 35 U. S. C. § 103(a)

The rejection of claims 1, 3, 5, 7, and 9-12 under 35 U.S.C. 103(a) as being unpatentable over Pecceu et al. (Gene, 97:253-258, 1991) and Selden et al. (U.S.

Patent NO. 6,083,725) in view of Colotta et al. (WO 9612022, April 25, 1996) is maintained. New claims 17 and 18 are also rejected on the same basis.

Applicants argue that Applicants have unexpectedly found that by fusing the sequence of icIL-1ra-II to the genomic growth hormone signal peptide, a secreted fully glycosylated active protein starting at amino acid +2A is obtained. Applicants further submit that such an unexpected result, in which the icIL-1ra-II protein starts at +2A instead of the predicted mixture of proteins at of +1M, +3L and +5D was obtained because the DNA encoding the growth hormone signal peptide used in the expression vector is genomic and therefore contains the sequence of the first intron of the human growth hormone gene.

Applicants' argument has been fully considered, but is not deemed to be persuasive for the following reasons. First, as clearly disclosed at page 17 of the specification (Example 10), sequence of the N-terminal amino acids indicated that the purified fraction separated from the culture supernatant contained two forms of icIL-1ra: a mixture of icIL-1ra-II proteins beginning at amino acid residue position +2 and +1 from the deduced start of translation on the icIL-1ra-II coding sequence. Thus, both the predicted product by the prior art and the product obtained by the Applicants are a mixture of proteins resulted from non-homogenous cleavage in icIL-1ra-II. Clearly, Applicants' assertion that by fusing the sequence of icIL-1ra-II to the genomic growth hormone signal peptide, a secreted fully glycosylated active protein starting at amino acid +2A, instead of the predicted mixture of proteins, is inaccurate.

Secondly, prima facie obviousness is not rebutted by merely recognizing additional advantages or latent properties present in the prior art. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known in vention. In re Wiseman, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979) (Claims were directed to grooved carbon disc brakes wherein the grooves were provided to vent steam or vapor during a braking action. A prior art reference taught noncabon disc brakes which were grooved for the purpose of cooling the faces of the braking members and eliminating dust. The court held the prior art references when combined would overcome the steam or vapor cause of the problem relied upon for patentability by applicants. Granting a patent on the discovery of an unknown but inherent function (here venting steam or vapor) "would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art." 596 F.2d at 1022, 201 USPQ at 661.).

In the instant case, the independent claim 9 is drawn to an expression vector for the production of an icIL-1ra-II protein beginning at amino acid residue position +2 from the deduced start of translation on the icIL-1ra-II coding sequence. Since full-length icIL-1ra-II protein and its encoding nucleic acid sequence (WO 9612022) and the genomic DNA sequence that encodes a human growth hormone signal peptide and contains the sequence of the first intron of the human growth hormone gene (see Fig. 10 of U.S. Patent NO. 6,083,72) are known in the art, it would have been obvious to one having ordinary skill in the art at the time the invention was made to construct an expression vector comprising the genomic DNA sequence taught by U.S. Patent NO. 6,083,72 and the DNA sequence encoding icIL-1ra-II with a reasonable expectation of success. Such

an expression construct would, under suitable expression conditions, necessarily produce a mixture of icIL-1ra-II proteins beginning at amino acid residue position +2 and +1 from the deduced start of translation on the icIL-1ra-II coding sequence. Thus, the instant case is analogous to the Wiseman case.

Furthermore, Applicants have the burden to establish that the differences in results are in fact unexpected and unovious and of both statistical and practical significance." Ex. Parte Gelles, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). In the Instant case, Applicants fail to establish both statistical and practical significance of the difference in the claimed expression vector and the expresion vector taught in the art when the references are combined. Applicants have not explained the importance of difference in a mixture of icIL-1ra-II proteins beginning at amino acid residue position +2 and +1 from the deduced start of translation on the icIL-1ra-II coding sequence versus a mixture of icIL-1ra-II proteins beginning at amino acid residue position +1M, +3L and +5D from the deduced start of translation on the icIL-1ra-II coding sequence regarding their biological activity or other properties.

Finally, to establish unexpected results, Applicants are required to submit a declaration or affidavit form (MPEP §716.02- §716.02 (g)). In the instant case, Applicants fail to provide such a declaration or affidavit under 37 CFR 1.132.

Claim Rejections Under 35 U. S. C. § 102 (b)

(i) The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(ii) Claims 9-12 are under 35 U.S.C. §102 (b) as being anticipated by Colotta et al. (WO 9612022, April 25, 1996).

Colotta et al. teach the full-length icIL-1ra-II protein, which is naturally expressed intracellularly in different cells, including human PMN, monocytes, and fibroblasts (Fig. 2). Colotta et al. also teach a method for producing the recombinant icIL-1ra-II (see, e.g., claim 10). The recombinant icIL-1ra-II showed a mass of approximately 25 KDa (line of 21 of page 10) by Western blot analysis on SDS gel (Fig. 3). Colotta et al. further teach a pharmaceutical composition comprising icIL-1ra-II (top of page 3 and 6th paragraph of page 5). Colotta et al. do not explicitly teach an icIL-1ra-II protein without the N-terminal methionine. However, it is well known in the art that N-terminal methionine processing and removal is a natural part of the maturation of the protein, as evidenced by Dalboge et al., FEBS 266:1-3, 1990, Rose et al., Analytical Biochemistry 165:59-65, 1987, and Flinta et al., Eur. J. Biochem. 154: 193-196, 1986. Thus, the reference of Colotta et al. meets the limitation of claims 9-12.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, can be reached on (571) 272-0961.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [Brenda.Brumback@uspto.gov]. All Internet e-mail

communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Ruixiang Li, Ph.D.
Examiner
August 30, 2004

JANET ANDRES
PRIMARY EXAMINER